PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference ZI-22267wo	**FOR FURTHER ACTION**	See Form PCT/IPEA/416
International application No. PCT/CH2004/000655	International filing date *(day/month/year)* 29.10.2004	Priority date *(day/month/year)* 30.10.2003
International Patent Classification (IPC) or national classification and IPC A61K9/20, A61K31/192		
Applicant ROCHE CONSUMER HEALTH AG et al.		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 7 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☐ *sent to the applicant and to the International Bureau)* a total of sheets, as follows:
      ☐ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

Date of submission of the demand	Date of completion of this report
27.05.2005	26.09.2005
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Baumgärtner, H Telephone No. +49 89 2399-

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/CH2004/000655

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3 and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4)
   - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

   Description, Pages

   1-32 as originally filed

   Claims, Numbers

   1-41 as originally filed

   Drawings, Sheets

   1/2-2/2 as originally filed

   ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	2-40
	No:	Claims	1, 41
Inventive step (IS)	Yes:	Claims	1-41
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-41
	No:	Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY (SEPARATE SHEET)

PCT/CH2004/000655

Re. item V

subject-matter

Cl. 1 non-effervescent tablet for oral administration of sodium naproxen

d37 specific composition
sodium naproxen - NaHCO3 - MC/croscarmellose
talc - Mg stearate

Cl. 41 process for producing a non-effervescent tablet for oral administration

The following documetns are referred to:

D1 US6165506 A 20001226 ELAN PHARMA INT LTD

Solid dose **nanoparticulate naproxen formulation** having a **high rate of dissolution** comprises:
(a) **naproxen** having an effective average particle size of less than 600 nm;
(b) a surface modifier adsorbed on the surface of (a); and
(c) an **alkali agent to increase the dissolution rate** of the nanoparticulate naproxen following administration where the formulation is prepared by having a surface stabilizer adsorbed on nanoparticulate naproxen composition surface, followed by drying the nanoparticules, an alkali agent is then added and the mixture is compressed to form a solid dose formulation (claim 1)
The composition of claim 1, wherein the **alkali agent is selected from the group consisting of sodium bicarbonate and potassium bicarbonate** (claim 3)

D2 US5034416 A 19910723 SMITH H J
Composition comprises (a) a carboxylic acid or one of its salts of either Ibuprofen,

Indomethacin, Diflunisal and **Naproxen**, and (b) a one to five molar excess of a **bicarbonate or carbonate** (cf. ex. 13/col.5)

D3 US6284274 B1 20010904 ALZA CORP
Dosage form for **delivering analgesics** comprises sodium, calcium or potassium carboxymethylcellulose, **alkali metal (bi)carbonate, alkaline earth (bi)carbonate**, hydroxypropyl(methyl)cellulose in specified amounts

Claim 4: A bilayer tablet comprising a **first layer comprising 50 ng to 1,000 mg of a non-opiate analgesic** selected from the group consisting of alfentanil, ketoprofen, buprenorphine, butorphanol, fentanyl, meperidine, methadone, nalbuphine, propoxyphene, natrexone, pentazocine, sufentanil, acetaminophen, aspirin, **ibuprofen, and naproxen** [...] and **second layer** possessing aqueous-fluid imbibing property comprising 30 to 225 mg of a carboxymethylcellulose of 75,000 to 2,500,000 molecular weight, 25 to 150 mg of a member selected from the group consisting of lithium carbonate, sodium carbonate, potassium carbonate, lithium bicarbonate, **sodium bicarbonate, potassium bicarbonate, and magnesium bicarbonate** [...]

D4 WO02083105 A2 20021024
Pharmaceutical composition useful for the treatment of inflammation comprises a **non-steroidal antiinflammatory active agent, a disintegrating agent and an anti-precipitation agent**

Refers to the **provision of a composition having enhanced absorption of NSAIDs**, which tend, to be poorly water soluble, as well as providing an improved concentration of the drug at the cellular level at the site of its action and envisages **to increase the absorption rate of such poorly water-soluble active agents by increasing the disintegration efficiency of the composition in tablet form, by accelerating the time and speed of the tablet disintegrating into molecules in solution, and by increasing the speed by which active agent is available in solution for absorption**
(p.3/l.23-29).

NSAIDs (or aspirin-like drugs) are typically categorized into six structural groups. [...] The **second are the propionic acid derivatives, including, but not limited to, ibuprofen, naproxen**, flurbiprofen, ketoprofen, fenoprofen, fenbufen, benoxaprofen and

suprofen (cf. p.3/l.33-34).
The **compositions** and methods are particularly suited to forming non-aqueous granulations and to **solid non-effervescent dosage forms**

The bicarbonate can be any bicarbonate salt that is pharmaceutically acceptable, preferably sodium or, potassium bicarbonate (p.9/l.31-34).

D5 WO02083110 A2 20021024
Animal model for testing absorption rate of medications, comprises mammal treated with two doses of anti-cholinergic agent

In accordance with one embodiment of the present invention, the composition contains **an NSAID**, preferably ibuprofen (hereinafter referred to as IB); a disintegration and dissolution agent, such as a bicarbonate, preferably sodium bicarbonate; and an ester of a fatty acid as an anti-precipitation agent. These ingredients are formed into a tablet or solid form, a tablet having enhanced disintegration into particles and subsequently enhanced dissolution of the particles into dispersed molecules in solution. In accordance with the present invention, **the bicarbonate is a disintegrator or disintegrating agent that increases the solubility of the NSAID**. The anti-precipitant provides an interface between lipid and aqueous phases (i.e., under gastric conditions) and prevents and/or reduces precipitation of the ibuprofen in the gastric environment (page 4/l.4-18).

he bicarbonate can be any bicarbonate salt that is pharmaceutically acceptable, preferably sodium or potassium bicarbonate. The alkali metal carbonate or bicarbonate used in accordance with the present invention may suitably comprise **sodium carbonate or bicarbonate or potassium carbonate or bicarbonate** either alone or mixed together.

Preferably, the alkali metal comprises sodium, thus sodium bicarbonate and sodium bicarbonate are preferred ingredients. The alkali metal carbonates may be supplied anhydrous or in varying degrees of hydration for example the monohydrate and decahydrate. Any of these forms may be used (page 6/l.30 - page 7/l.4)

Solid **non-effervescent compositions** are preferred compositions of the present invention. The preferred compositions are preferably formed into a tablet.

Formulation 2 (tablet, wet granulation): Ibuprofen 200 g, sodium bicarbonate 80 g, gelucire 15 g, hypromellose 20 g, pre-gelatanized starch 168.4 g; microcrystalline cellulose 84.0 g; sodium croscarmellose 28.0 g; and magnesium stearate 3.0 g. Each tablet weighed 299 mg

and contained 100 mg ibuprofen (page 13-14, ex. 2/formulation 2)

D6 WO9730699 A2 19970828 BOOTS CO PLC

solid, **non-effervescent**, compressed dosage form comprising: (a) at least 35 wt.% **ibuprofen** medicament; and (b) a **carrier comprising**: (i) a compressible **filler** component combined; with (ii) a **disintegrating component** is characterised in that the carrier material includes an **alkali metal carbonate or bicarbonate** in an amount such that the dosage form has a crushing strength of 6.5-15 kP and a **disintegration time of < 10 minutes** (claim 1) example 1/p.20 : ibuprofen, microcrystalline cellulose, croscarmellose, colloidal silicon dioxide, stearic acid, magnesium stearate

Novelty (i), Inventive Step (ii) und Industrial Applicability (iii) - Art. 33 (1)-(4)

i.
The subject-matter of claim 1 and 41 is not novel in view of D1-D3.

ii.
The problem appears to be the provision of further improved oral naproxen formulations, the improved property of which is mainly due to the reduced disintegration time (cf. description/page 27/l.14)

D1, D4 - D6 are already concerned with the same problem, solving it by adding an alkali metal salt or the like which is discuseed at length to be responsible for the resulting improved disintegration time.

Thus no difference remains between the prior art and the claimed formulation at presence, i.e. the claims do not fulfil the requirements of inventive step.